Brain death/death by neurologic criteria: What you need to know

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ABSTRACT: Since the beginning of time, man has been intrigued with the question of when a person is considered dead. Traditionally, death has been considered the cessation of all cardiorespiratory function. At the end of the last century a new definition was introduced into the lexicon surrounding death in addition to cessation of cardiac and respiratory function: Brain Death/Death by Neurologic Criteria (BD/DNC). There are medical, legal, ethical, and even theological controversies that surround this diagnosis. In addition, there is no small amount of confusion among medical practitioners regarding the diagnosis of BD/DNC. For families enduring the devastating development of BD/DNC in their loved one, it is the duty of the principal caregiver to provide a transparent presentation of the clinical situation and clear definitive explanation of what constitutes BD/DNC. In this report, we present a historical outline of the development of BD/DNC as a clinical entity, specifically how one goes about making a determination of BD/DNC, what steps are taken once a diagnosis of BD/DNC is made, a brief discussion of some of the ethical/moral issues surrounding this diagnosis, and finally the caregiver approach to the family of a patient who had been declared with BD/DNC. It is our humble hope that with a greater understanding of the myriad of complicated issues surrounding the diagnosis of BD/DNC that the bedside caregiver can provide needed closure for both the patient and the family enduring this critical time in their life. (*J Trauma Acute Care Surg.* 2024;97: 165–174. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Brain death; death by neurologic criteria; criteria; clinical examination; imaging.

Death, as it was traditionally defined in medicine, relied on the cessation of cardiorespiratory function. A patient was not dead until all circulation had stopped. However, with the advent of positive-pressure ventilation and cardiopulmonary resuscitation, lung and heart function could be artificially supported for extended periods of time, linking these patients to cardiopulmonary support technology maintaining a comatose state.[1] It was not until 1959 when Mollaret and Goulon published their theory "le coma dépassé," now referred to as Brain Death/Death by Neurologic Criteria (BD/DNC), that the current concept of death in medicine was born.[2] In their landmark publication, Mollaret and Goulon described a patient without activity on an electroencephalogram, lacking spontaneous respiration, and requiring constant norepinephrine administration to maintain blood pressure. This patient was in a 'state beyond coma' and it was understood that without constant medical attention, the heart would stop, and the patient would die.[3] This paper laid the foundation for the understanding in medicine that cessation of neurological function is as important as cessation of cardiorespiratory function for determining death. Nearly a decade later in 1968, the Harvard Brain Death criteria was created to set forth clinical standards required for the diagnosis of BD/DNC.[4] A patient could now be declared dead if they fit into one of two categories: (1) cessation of cardiorespiratory function (i.e., death of the body), and (2) BD/DNC (i.e., death of the mind). However, a legal basis for establishing neurological death was not established until the early 1980s with the Uniform Determination of Death Act. This law created a legal separation between cardiorespiratory demise and BD/DNC, stating that BD/DNC alone was sufficient to declare death. Under this statute, BD/DNC is equivalent to death by cardiac arrest. The Uniform Determination of Death Act is accepted in all 50 states, the District of Colombia, as well as by the American Medical Association, and American Bar Association. Despite being an accepted form of determination for death, the criteria for determining BD/DNC varies between states and even among institutions. In 2020, an international panel of clinicians was convened in the World Brain Death Project to provide a set of general guidelines to limit the variability in diagnosing BD/DNC.[5] The recommendations set forth by this panel provide the foundation for current institutional BD/DNC protocols (Table 1).

Pathophysiology of BD/DNC

BD/DNC as a Result of Increased Intracranial Pressure (ICP)

The brain, while only accounting for 2% of total body weight, requires approximately 20% of resting oxygen consumption (up to 50% of resting oxygen consumption in children) and 15% of cardiac output. This high oxygen demand by the brain means that cerebral oxygen stores are insufficient to support even brief interruption of oxygen delivery, and even at its peak, anaerobic metabolism is insufficient to maintain cerebral function. Suspension of cerebral perfusion results in loss of consciousness within 10 seconds.[8] Cerebral perfusion may be described by Ohms law: $Q = \Delta P/R$. Which states that flow (Q) is equal to the pressure gradient between inflow and outflow (ΔP) divided by resistance (R). In the context of the brain, mean arterial pressure (MAP) represents inflow pressure, and intracranial pressure (ICP) represents outflow pressure. Assuming a constant resistance, flow or cerebral perfusion pressure (CPP) can be calculated using the equation: $CPP = MAP - ICP$. A CPP of zero means the brain has a complete lack of perfusion. This is important in the context of BD/DNC as BD/DNC cannot be diagnosed if there is maintained perfusion to the brain.[9]

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TABLE 1. Differences in the Classification of BD/DNC Over Time

	Harvard Brain Death Criteria[6]	Uniform Determination of Death Act[7]	World Brain Death Project[5]
Year published	1968	1980	2020
Purpose	Define irreversible coma as a new criterion for death	Provide a general legal, not medical, standard for determining death in all instances	To create a consensus statement for recommendations of the minimum criteria required to diagnose BD/DNC
Criteria	1. Patient must be unreceptive and unresponsive. The patient is unaware of external stimuli and their own inner needs 2. No spontaneous movement or respiration 3. No brainstem reflexes	Death is either: Irreversible cessation of cardiorespiratory function OR Irreversible cessation of all function in the entire brain, including brainstem	1. Determination that the patient has experienced a devastating, irreversible, brain injury resulting in complete loss of brain function 2. Exclusion of confounders or reversible conditions 3. No awareness or arousal to external stimulation (noxious visual, auditory, and tactile) 4. Absence of brainstem reflexes 5. Absence of brain-mediated motor responses to noxious stimulation of the extremities
Tests recommended	1. Eliciting painful stimuli 2. Observing the patient for at least 1 h for spontaneous respiration or movement, especially in response to pain, touch, sound, or light. 3. Rudimentary apnea test (turn off mechanical ventilation for 3 minutes and monitor for spontaneous respirations) 4. Testing of the pupillary reflex 5. Ocular movement testing (cold caloric test and monitoring for blinking) 6. No evidence of postural activity (decerebrate or otherwise) 7. Monitor for absence of swallowing, yawning, and vocalization 8. Absence of corneal reflex 9. Absence of pharyngeal reflex 10. Absence of stretch of tendon reflexes and plantar reflex	N/A	1. Noxious visual, auditory, and tactile stimulation 2. Testing of the pupillary reflex 3. Testing of the oculocephalic reflex 4. Testing of the oculovestibular reflex 5. Testing of the corneal reflex 6. Testing of the motor response of face and extremities 7. Testing of the gag reflex 8. Testing of the cough reflex 9. Apnea test
Ancillary studies recommended	• Flat EEG • Repeated examinations over 24 h or longer to establish irreversibility	N/A	• DSA • Radionuclide studies • TCD
Confounding conditions mentioned	• Hypothermia • CNS depressants such as barbiturates	N/A	• Pharmacologic paralysis • CNS depressing medications, including toxins • Alcohol intoxication • Severe metabolic, acid-base, and endocrine abnormalities • Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Facial trauma • Basilar skull fracture with hemotympanum • Cervical spine injury • Pulmonary injury/disease • Anophthalmia
Who is responsible for declaring BD/DNC?	Physician-in-charge, in consultation with one or more physicians involved in the patients care	N/A	Practitioners licensed to independently practice medicine trained in determination of BD/DNC and in the counseling of families of patients at the end of their life. These practitioners should have experience managing devastating brain injuries
Time of death mentioned?	No	No	Yes, time noted by the laboratory when the ABG resulted OR Time ancillary study was formally interpreted OR Time second clinical examination is completed

CNS, central nervous system.

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TABLE 2. Clinical Examination for BD/DNC[9,11] *

	How to Conduct	Results That Indicate BD/DNC	Physiology	Confounders/ Contraindications
Response to noxious stimuli	Apply deep pressure to: 1. The temporomandibular joint 2. The supraorbital notch bilaterally 3. The sternum 4. All four extremities both proximally and distally	Noxious stimuli should not result in any movement of the face. Noxious stimuli below the foramen magnum may elicit spinal cord reflexes	1 and 2: Assesses damage to the trigeminal nerve (cranial nerve V) 3 and 4: Assesses damage to brainstem through activation of peripheral nerves	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • Facial trauma • Cervical spine injury
Spontaneous respiration	Observe patient for spontaneous respirations on the ventilator	No spontaneous respirations	Assesses damage to medulla oblongata and lower pons, specifically the central pattern generator	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality
Pupillary reflex†	Shine a bright light into the eye of the patient to assess for pupillary constriction	No pupillary response to light	Assesses structural integrity of midbrain	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • Facial trauma • Anophthalmia
Corneal reflex†	Touch the patient's cornea (not conjunctiva) with cotton swab or tissue	No motor response to this stimulus	Assesses structural integrity of the pons	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • Anophthalmia
Oculovestibular reflex (cold caloric) †	Irrigate the inner ear with at least 30 mL of cold water (0°C). The patient should be supine with the head of the bed at 30° from the horizontal. Irrigation should last 60 s and be repeated on each ear with a minimum of 5 min between injection episodes.	No response (nystagmus) to irrigation	Assesses damage to afferent fibers, vestibular nuclei, oculomotor nerves, and internuclear connections	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • Basal skull fracture with hemotympanum • Facial trauma • Anophthalmia
Oculocephalic reflex (dolls eyes) †	Place both hands on the patient's head and turn the head to one side and observe movement of the eyes. Repeat for both left and right side	Lack of eye movement in response to examination	Assesses damage to afferent fibers, vestibular nuclei, oculomotor nerves, and internuclear connections	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • Cervical spine injury • Facial trauma • Anophthalmia

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TABLE 2. *(Continued)*

	How to Conduct	Results That Indicate BD/DNC	Physiology	Confounders/ Contraindications
Cough reflex†	Deep suctioning of endotracheal tube	Patient does not cough	Assesses damage to the medulla interrupting fibers of cranial nerves IX and X	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality
Gag reflex†	Stimulate posterior pharynx with tongue blade	Patient does not gag	Assesses damage to the medulla interrupting fibers of cranial nerves IX and X	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality
Apnea testing	*Prerequisites:* • Last clinical examination in BD/DNC survey • Prior tests indicate BD/DNC • Normothermia • Euvolemia • SBP > 100 • MAP >60 • Normal $PaCO_2$ • ABG drawn prior to test *Exam*ination • Begin examination by preoxygenating the patient with 100% O_2 via ET tube. The PaO_2 must be ≥200 mm Hg and continuous PaO_2 and SpO_2 monitoring must be conducted prior to disconnecting the ventilator. • Disconnect ventilator and observe for respiratory movement for 8–10 min until $PaCO_2$ ≥ 60 mm Hg on the $ETCO_2$ monitor. • After ventilation is restarted, draw a repeat ABG. If $PaCO_2$ is not ≥60 mm Hg on point-of-care testing, the apnea test should be continued for another 5 min, repeating the ABG after this time • Where point-of-care testing is not used, the test is repeated for 15 min after which the patient is returned to normocarbia and is oxygenated again	No respiratory efforts by the patient and the repeat ABG results with a $PaCO_2$ > 60 mm Hg	Assesses damage to medulla oblongata and lower pons, specifically the central pattern generator	• Hypothermia • Muscle paralysis • Sedation/analgesia • Hypoxia • Hypotension • Hypoglycemia • Endocrine/metabolic abnormality • High cervical spine injury • Pulmonary disease/injury *Discontinue test if:* • SBP < 100 mm Hg or MAP <60 despite initiation of fluids/inotropes/vasoactive drugs • O_2 saturation < 85% • Cardiac dysrhythmias occur

*Prior to beginning the clinical exam, an absence of any toxic, metabolic, or pharmacologic confounding conditions that may suppress brain function must be determined.
†Patient should be normally ventilated while testing brain stem reflexes. SBP, systolic blood pressure; ET, endotracheal.

The Monro-Kellie doctrine points out that the brain is highly sensitive to changes in ICP, and that the skull in adults, and children with fused cranial bones, is a noncompliant structure that operates as a "closed box." This means that the total volume of the intracranial contents must remain constant and any dysregulation in the volume of the brain, blood contained in the cranium, or cerebrospinal fluid (CSF) must be offset by the other two entities to maintain normal ICP. The brain has compensatory capacity to prevent ICP changes, the first being the shift of CSF from the intracranial to the spinal subarachnoid compartment. However, due to the relatively small volume of CSF in the brain, this compensatory mechanism will only be able to offset small intracranial volume changes as CSF represents only 5% of total intracranial volume, with brain parenchyma occupying 85% and blood 8% to 10% of intracranial volume. The brain compensates for increased ICP through reduction of capacitance of the cerebral veins and dural sinuses. These compensatory mechanisms are quickly overwhelmed and significant elevations in ICP can result in CPP dropping to critical levels causing aseptic cellular necrosis and subsequent autolysis of the brain. However, CPP does not have to be zero to be deemed critical. When CPP falls in the setting of extremely elevated ICP, the cerebral vascular bed will reach its critical closing pressure and collapse as the pressure in the cerebral vasculature is insufficient to maintain vascular patency in the setting of high external pressure (ICP).[9]

BD/DNC After Cardiac Arrest

A 2016 meta-analysis found that 8.9% of patients that are initially resuscitated after cardiac arrest develop BD/DNC.[10] Cases of cardiac arrest are unique in the sense that they do not

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always result in the complete cessation of cerebral perfusion. In animal models, delay of CPR by more than 6 minutes was found to be consistently associated with loss of brainstem function and cessation of activity on an EEG. There are two main mechanisms by which BD/DNC occurs because of hypoxic-ischemic injury. The first mechanism is ischemic neuronal death involving the selective loss of acidophilic neurons in specific brain regions, particularly the CA1 subfield pyramidal cells of the hippocampus, Purkinje cells of the cerebellum, small and medium-sized neurons of the striatum, and layers three, five, and six of the neocortex. This neuronal loss is accompanied by the activation of reactive astroglia cells. If this type of neuronal death is sufficient, it can begin to kill the more resistant brainstem neurons without increasing ICP. These events may result in the patient meeting clinical criteria for BD/DNC, but with maintenance of cerebral perfusion. In these cases, care must be taken to rule out potentially reversible causes of neuronal dysfunction such as hypothermia, sedatives, neuromuscular blockers, or metabolic disturbances. A second mechanism is BD/DNC occurring after cardiac arrest because of microinfarcts associated with perivascular and diffuse tissue sponginess. These lesions are multifocal, perivascular, and are present in multiple layers of the brain, most commonly appearing in the cerebral watershed regions. If microinfarcts are the predominant lesions, a pattern of multifocal watershed cerebral infarcts will result in progressive cytotoxic edema with a subsequent increase in ICP and eventual BD/DNC as a result of reduced cerebral perfusion.[9]

Caring for the Family Before the Diagnosis of BD/DNC

In the case of severe brain injury, regardless of a potential progression to brain death, the family must be informed in no equivocal terms that, for this patient, life may never be the same. When the diagnosis of BD/DNC is suspected, but not yet confirmed, the tone of the conversation with family must reflect the severity of the situation. A discussion must happen between the family and the team of consultants, usually neurosurgery and surgical intensive care unit (SICU) intensivists. We recommend the care team prepare for this discussion prior to meeting with the family to outline what will, and more importantly, will not be said. Offering the family hope, while it may be what the family wants to hear, is inappropriate when it is too early to accurately prognosticate. It is recommended to provide an observation period after injury before a BD/DNC examination be conducted[5] for clinicians to assess the patient and rule out any confounding conditions that may mimic BD/DNC.

Clinical Examination

Brain death is a clinical diagnosis, that is, it is an objective finding based on the results of various clinical examinations. While the number of examinations required to identify BD/DNC may vary between institutions, the World Brain Death Project has established the minimum criteria to diagnose BD/DNC[5] (Table 2).

The clinical examination to determine BD/DNC includes checking for absent response to painful stimulus in the extremity, truncal, and facial muscle groups; determining if the patient will breathe spontaneously, and evaluating the absence of brainstem reflexes (oculovestibular, corneal, pupillary, oculocephalic, cough, and gag). If the listed tests indicate no brainstem function, apnea testing should be performed. It is important to note that if any part of this clinical examination cannot be completed, ancillary testing must be performed to obtain a definitive diagnosis.

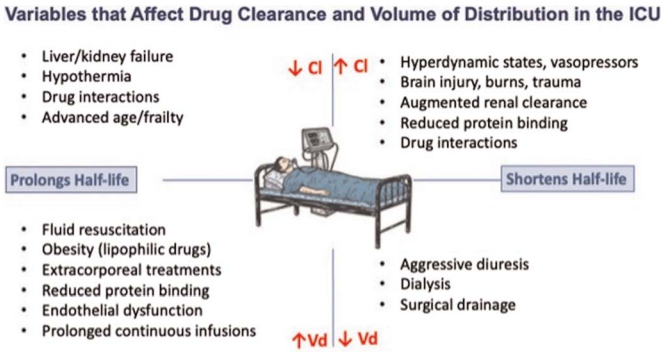

Figure 1. Variables that impact drug clearance and volume distribution. Cl, clearance; ICU, intensive care unit; V_d, volume of distribution. (Figure reprinted from Kanji S, Williamson D, Hartwick M. Potential pharmacological confounders in the setting of death determined by neurologic criteria: a narrative review. *Can J Anaesth*. 2023;70(4):713–723. Accessed December 29, 2023. Used under Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) Artwork credit: Viktoriia Panchenko, www.dreamstime.com).

Prior to beginning the clinical examination, absence of any toxic, metabolic, or pharmacologic confounding conditions that may suppress brain function must be determined. A position statement published by the American College of Medical Toxicology challenges the popular notion that waiting five half-lives of a specific drug is sufficient to allow use of the clinical examination, in isolation, to determine BD/DNC. There are a multitude of variables that may impact drug clearance and volume distribution in these patients (Fig. 1), and while waiting five half-lives in some situations may remove enough drug to move concentrations below clinically significant levels, in cases of severe overdose five half-lives (3% of the original drug amount) may still cause clinically significant impairment to brain function.[12] Further, various conditions may make aspects of the clinical examination unreliable. This is where ancillary testing, specifically brain perfusion studies, are most useful.

Spontaneous Respiration

The patient should be assessed for spontaneous respirations on the ventilator. If the patient is breathing spontaneously, even if they require ventilatory support, they do not meet the criteria for BD/DNC.

Brainstem Reflexes

The neuroanatomical basis of brainstem reflexes is well understood and offers the clinician the ability to test every aspect of the brainstem. To ensure a reliable examination, the patient should be normally ventilated before testing.

Pupillary

Testing of the pupillary reflex is done to assess the structural integrity of the midbrain. Damage to the midbrain may

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result in bilateral oculomotor paralysis resulting in the absence of the pupillary light reflex.[9] This test involves shining a bright light in the eye of the patient to assess for reactive pupillary constriction. Ideally, a pupilometer will be used for this assessment as it is an objective measurement of pupillary response and will observe minute movements that may be missed by clinicians.

Corneal

Testing of the corneal reflex is done to assess the structural integrity of the pons. Damage to this region may affect the afferent trigeminal fibers as well as the efferent facial nerve fibers responsible for the corneal blink reflex and any facial motor response or grimacing in response to noxious stimulation of the trigeminal area.[9] Corneal reflex evaluation involves touching the patient's cornea (not conjunctiva) with a cotton swab or tissue. In healthy patients, this contact will cause closure of the eyelid. In patients with damage to the brainstem there will be no motor response to this stimulus.

Oculovestibular (Cold Caloric)

Testing of the oculovestibular reflex is done to assess damage to afferent fibers, vestibular nuclei, oculomotor nerves, and internuclear connections.[9] This reflex is tested via cold caloric testing. Cold caloric testing involves irrigation of the inner ear with at least 30 mL of cold water (0° C). With the patient laying supine, position the patient's head at 30° from the horizontal to place the semicircular canals in a vertical position. Irrigation should last 60 seconds and be repeated on each ear with a minimum of 5 minutes between injection episodes. If the brainstem is intact, nystagmus will occur where both eyes slowly move toward the irrigated ear then quickly move away. An asymmetrical response will only have one eye respond to the cold-water irrigation, the other eye will remain fixed at the midline. In severe brainstem damage, both eyes will remain fixed in the midline position and will not respond to the cold-water irrigation. Any response to the irrigation is inconsistent with BD/DNC. It is important to note that neuromuscular blockers and barbiturates can inhibit this reflex, mimicking brainstem damage.

Oculocephalic (Doll's Eyes)

Testing of the oculocephalic reflex or "doll's eyes" reflex is done to assess damage to afferent fibers, vestibular nuclei, oculomotor nerves, and internuclear connections.[9] The oculocephalic reflex is perhaps the most complicated of all the brainstem reflexes. Initially, confirm that the patient has no cervical spine injury. If there is a cervical spine injury, this test should not be performed, and ancillary testing is required to diagnose BD/DNC. Once the cervical spine is cleared place both hands on the patient's head and turn the head to one side and observe movement of the eyes. If the patient has an intact brainstem response, the eyes will move contralateral to the movement of the head. The test should include turning the patient's head both left and right, moving the head up and down is optional. Lack of eye movement during this test suggests BD/DNC.

Cough

Testing of the cough reflex is done to assess damage to the medulla interrupting fibers of cranial nerves IX and X.[9] The cough reflex is tested through deep suctioning of the endotracheal tube. If the patient has an intact brainstem, this stimulation will cause cough.

Gag

Testing of the gag reflex is done to assess damage to the medulla interrupting fibers of cranial nerves IX and X.[9] This test involves stimulating the posterior pharynx with a tongue blade. In patients with an intact brainstem this stimulation will cause them to gag, lack of a gag reflex suggests BD/DNC.

Apnea Testing

Apnea testing is conducted to test the medulla oblongata and lower pons, specifically the central pattern generator and its sensitivity to changes in CO_2 mediated CSF acidosis to drive spontaneous respiration.[9,11] Apnea testing should always be the last clinical examination in the BD/DNC survey and should only be conducted if all prior testing is consistent with brain death (BD). Apnea testing should not be conducted in patients with high cervical spinal cord injury. Prior to apnea testing being conducted, the patient must be normothermic, euvolemic, have a systolic blood pressure >100 mm Hg or MAP >60, have a normal $PaCO_2$ (35–45 mm Hg); an arterial blood gas (ABG) should be drawn prior to starting the apnea test. There must be a confirmed absence of hypoxia and any confounding conditions that may mimic BD/DNC or suppress respiratory drive.

To perform the apnea test, the patient must be preoxygenated with 100% oxygen via an endotracheal tube and their arterial oxygen tension (PaO_2) levels must reach 200 mm Hg. $PaCO_2$ and SpO_2 must be monitored with pulse oximetry and continuous end tidal CO_2 measurement ($ETCO_2$). Begin the test by disconnecting the ventilator and observe for respiratory movement for 8 minutes to 10 minutes until $PaCO_2 \geq 60$ mm Hg on the $ETCO_2$ monitor. After ventilation is restarted, a repeat ABG should be drawn. If $PaCO_2$ does not reach target levels (≥60 mm Hg) on point-of-care testing, the apnea test should be continued for another 5 minutes, repeating the ABG after this time. Where point-of-care testing is not used, the test is repeated for 15 minutes after which the patient is returned to normocarbia and is oxygenated again.[11] Testing should be discontinued if spontaneous respirations occur, systolic blood pressure falls below 100 mm Hg or MAP is less than 60 mm Hg despite the initiation of fluids/inotropes/vasoactive drugs, oxygen saturation falls below 85%, or any cardiac dysrhythmias occur. The apnea test is considered positive (i.e. supports the diagnosis of BD/DNC) if there are no respiratory efforts by the patient and the repeat ABG results with a $PaCO_2 > 60$ mm Hg.

Ancillary Studies

Due to the complexities of various patient populations, a clinician may consider additional testing to diagnose BD/DNC. Concurrent clinical conditions that may limit the performance or interpretation of the clinical examination include cervical spine or spinal cord trauma, ocular trauma, recent therapeutic hypothermia after cardiac arrest, administration of sedative drugs, and hypoxia or hypotension during the apnea test. While ancillary studies are helpful adjuncts to the clinical examination, they are not a replacement for it, and it is important to discuss the limitations of these tests with family. An ideal ancillary study should

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TABLE 3. Ancillary Studies for BD/DNC[11,13]

	Type of Examination	Results That Indicate BD/DNC	Sensitivity/Specificity	Recommended by WBDP
DSA	Brain perfusion study	Absence of contrast dye in intracranial vessels	100%/100%	Yes
SPECT	Brain perfusion study	Absence of metabolic uptake of radionuclide	*SPECT:* 88.4%/100% *Planar (patient transport not feasible):* 77.8%/100%	Yes
TCD*	Brain perfusion study	Absence of cerebral perfusion velocity	90%/98%	Yes
CTA	Brain perfusion study	No cerebral perfusion	52–97%/100%	No
Second physician clinical test	Clinical examination	Second examination confirms BD/DNC	N/A	No, conditional/weak recommendation for one clinical examination
EEG	Records brain electrical activity	No detectable electrical activity	53–80.4%/97%	No

*Normal ventilation is required for the most accurate TCD imaging.
WBDP, World Brain Death Project.

meet the following five criteria: (1) no false positives (patients diagnosed with BD/DNC that subsequently recover); (2) has the ability to independently diagnose BD/DNC; (3) maintains accuracy regardless of confounders such as drugs or metabolic disturbances; (4) is standardized across institutions in technology, technique, and interpretation of results; and (5) is easily learned and can be utilized in all critical care settings, not just specialty academic medical centers. The following ancillary studies are recommended by the World Brain Death Project for the diagnosis of BD/DNC[13] (Table 3).

Digital Subtraction Angiography

Digital subtraction angiography (DSA) is historically considered the gold standard of ancillary testing with 100% specificity and 100% sensitivity for diagnosing BD/DNC, although the claim of 100% sensitivity is challenged when patients meet all clinical criteria for BD/DNC while maintaining cerebral perfusion. Digital subtraction angiography is a technically challenging and invasive procedure that carries the risk of thrombosis, vasospasm, and nephropathy due to the contrast used.[13] Digital subtraction angiography requires taking a "mask image" prior to the injection of contrast dye. This mask image contains only the bony structures and surrounding tissue. A subsequent image is then taken after the dye has been injected and the mask image is "subtracted" from the contrast containing image. After subtraction of the mask image, only the contrast containing blood vessels remain without occlusion from other structures. Absence of contrast in the image is consistent with BD/DNC.

Single-Photon Emission Computerized Tomography

Single-photon emission computerized tomography (SPECT) is an ancillary nuclear perfusion study used to assess the perfusion of the brain using a radioactive tracer injected into the patient's blood stream (Figs. 2 and 3). On a SPECT scan, loss of blood flow indicates BD/DNC. The presence of small amounts of cerebral perfusion does not confirm brain function. This test is less time and resource intensive than DSA but maintains similar sensitivity (SPECT, 88.4%; DSA, 100%) and specificity (SPECT, 100%; DSA, 100%). However, the claim of 100% specificity for the SPECT scan is based on experimental data and should be interpreted with caution.[4,13] Prior to the initiation of a SPECT scan the patient must have a stable blood pressure and any reversible biochemical abnormalities should be corrected. This scan involves moving the patient to a scanner so the benefits and risks of moving the patient should be assessed prior to transport. If the patient cannot tolerate transport, planar imaging may be conducted at the cost of reduced sensitivity (SPECT, 88.4%; planar, 77.8%).[13] General tips for performance of this scan include normal ventilation the patient. Hyperventilation will reduce cerebral perfusion. Confirm the absence of barbiturates. Place a tourniquet at the top of the skull just above the eyebrows and ears to limit blood flow from the scalp that may cause confusion when reading the scan.[14]

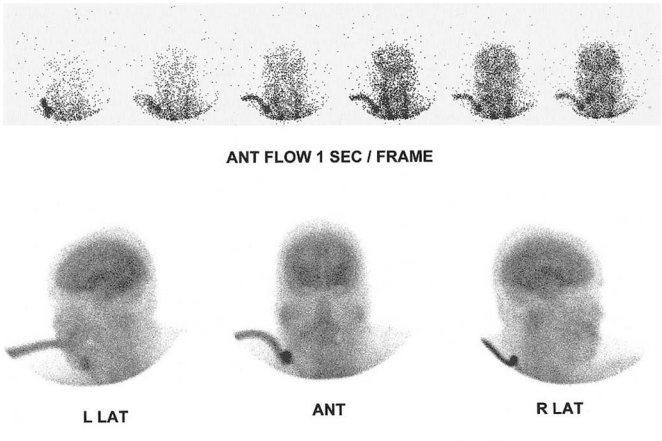

Figure 2. Radionuclide scan of a healthy patient. Preservation of cerebral flow and metabolism. Radionuclide cerebral angiogram (above) following the intravenous bolus injection of 25 mCi (950 MBq) Tc-99m HMPAO shows flow within the anterior and middle cerebral artery distributions. Planar 500 K "static" images (below) performed immediately thereafter show localization of the radiopharmaceutical within both cerebral hemispheres. Cerebellar hemispheric metabolism also is preserved but appears decreased. Tc-99m HMPAO, hexamethylpropyleneamine oxime (figure and description reprinted from Conrad GR, Sinha P. Scintigraphy as a confirmatory test of brain death. *Semin Nucl Med.* 2003;33(4):312–323. Copyright (2003), with permission from Elsevier).

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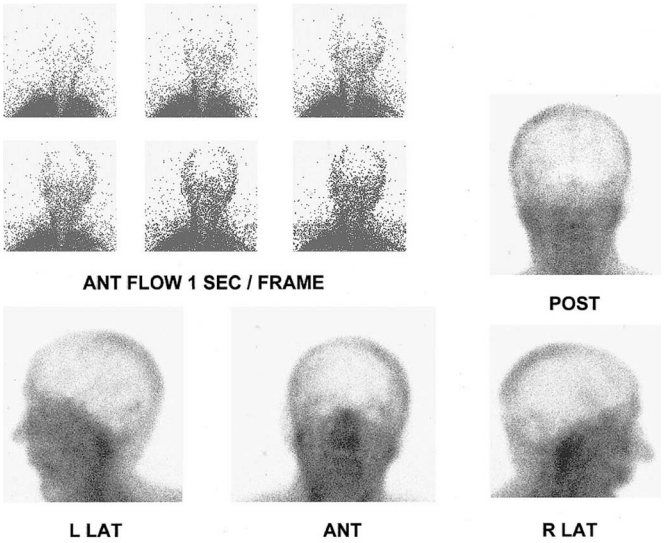

Figure 3. Radionuclide scan of a brain-dead patient. Brain death in a 58-year-old who had massive subdural hematoma. First pass radionuclide cerebral angiogram with intravenous bolus of Tc-99 m HMPAO (upper left) shows flow in the common carotids, as well as flow within the external carotid artery distributions. The anterior and middle cerebral artery complexes were not visualized out to 1 minute. Subsequent planar imaging (below and right) show no radiopharmaceutical localization within the cerebral cortices, basal ganglia, thalami, or cerebellar hemispheres. The sagittal and transverse venous sinuses can be identified on the posterior projection images, and the sigmoid sinuses are just discernable on the lateral projection images (figure and description reprinted from Conrad GR, Sinha P. Scintigraphy as a confirmatory test of brain death. *Semin Nucl Med*. 2003;33(4):312–323. Copyright (2003), with permission from Elsevier). Tc-99m HMPAO, hexamethylpropyleneamine oxime.

Transcranial Doppler (TCD)

Transcranial Doppler (TCD) is a noninvasive method for assessing cerebral perfusion velocity at the bedside using ultrasound. To assess BD/DNC using TCD, two examinations imaging both the anterior and posterior of the brain must be done separated by at least 30 minutes. Anterior perfusion is assessed through the use of the acoustic temporal bone windows, although this cannot be performed in 10% of the population due to natural lack of an adequate temporal acoustic window.[4] Posterior perfusion is assessed though insonation of the basilar and vertebral arteries to assess brainstem perfusion. Assessment of these arteries, while not universally done, is essential to obtain the highest sensitivity (90%) and specificity (98%) during the TCD examination.[13] Due to its measure of cerebral perfusion velocity, normal ventilation is required for accurate results of TCD imaging. While the TCD does require expertise in ultrasound, it is an attractive option as an ancillary test as it is less technically involved than DSA or SPECT.

Computerized Tomographic Angiography

Computerized tomographic angiography (CTA) requires intravenous injection of contrast to observe cerebral perfusion. This examination can be performed quickly and is available in nearly every hospital where a BD/DNC examination may occur. While CTA was not an endorsed ancillary study by the WBDP in 2020, this was due to the lack of strong evidence, not its inability to diagnose BD/DNC. Current literature presents the CTA-based-4-point scoring system as an appropriate ancillary study to diagnose BD/DNC in both adults and children,[15] with high sensitivity and specificity.[16] Computerized tomographic angiography is currently endorsed as the ancillary test of choice by a variety of stakeholder professional organizations in the United Kingdom[17] and it is expected to replace DSA as the gold standard of BD/DNC ancillary testing.

Second Physician Clinical Test

Clinical examinations by a second independent physician may be conducted to confirm the diagnosis of BD/DNC without the use of ancillary testing. The examinations conducted do not necessarily require a waiting period between tests given the prerequisite of irreversibility for BD/DNC. In cases of concurrent testing, only one apnea test is recommended. Should a waiting period be utilized between the examinations, a complete second physical examination and apnea test are required to confirm BD/DNC.[11]

Electroencephalography

Compared with other ancillary studies that examine blood flow to the brain, electroencephalography (EEG) monitors the electrical activity of the brain. However, utility of EEG as an ancillary test for determining BD/DNC is limited as it can only reliably detect cortical brain activity. It is not recommended to use EEG as an ancillary study unless to confirm the presence of subtle electrical activity in the brain such as covert consciousness.[4]

Spinal Cord Reflexes

Reflexive movements emanating entirely from the spinal cord, totally independent of any higher cortical function, may give caregivers and family members the erroneous impression that the patient is not dead by BD/DNC. These reflexes are present in 13% to 75% of brain-dead patients[11] and range from simple movements to complex triple flexion with the patient rising out of bed (Lazarus sign). The family should be reassured that spinal cord reflexes do not cancel a determination of BD/DNC.

Declaration of BD/DNC

Once a patient meets BD/DNC criteria they are considered legally dead, and the following individuals should be informed according to local laws and policies: attending physician, family, the local organ procurement agency (OPA), medical examiner, and the hospital chaplain or pastoral care team. The time of death for these BD/DNC patients, in cases without ancillary testing, is the time the ABG reached the target $PaCO_2$ as documented by the laboratory. If ancillary testing is conducted, time of death is when the test is formally read and documented on their report. If more than one examination is conducted, the time of death is when the second examination is completed.[18] Once the discussion of BD/DNC has occurred, the patient is disconnected from the ventilator. There are only three situations where a patient may remain on a ventilator after the diagnosis of BD/DNC:

1. In preparation for organ procurement.
2. In a pregnant patient to allow the fetus to mature for delivery.

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3. To allow next of kin a limited period, usually not more than 72 hours, for out-of-town family members to come and see the patient.

Ethical/Legal Considerations

Difficult ethical challenges arise when families refuse to accept the determination of BD/DNC. Family permission is not required to conduct a BD/DNC examination. This can be a point of contention between family and the care team. Here, the hospital ethics committee and chaplains can be an invaluable resource. What adds to confusion and difficulty is the news stories of patients that have been diagnosed with BD/DNC and subsequently recovered or families who have successfully resisted the diagnosis of BD/DNC and moved their loved one to another state, such as in the case of Jahi McMath.[19] In this case, Ms. McMath was declared BD by neurologic examination, EEG, and radionucleotide scan showing intracranial circulatory arrest. Nearly 10 months later, her MRI scan showed surprising gross integrity of cortex, basil ganglia, and upper brainstem.[20] These findings supported that there was minimal blood flow (below the threshold to detect on a radionucleotide scan) sufficient to maintain widespread neuronal viability.

The American Academy of Neurology has released a position paper to facilitate discussion of BD/DNC with families.[21] In this paper the Academy declared that while patient and family autonomy is to be respected, it is not appropriate to provide desired, but unjustified, medical treatment. Further, they state there is a potential to harm the patient, the family, or the healthcare team in making indefinite accommodations to family to keep the patient on ventilator support. This includes mistreatment of a newly dead patient, deprivation of patient dignity, provision of false hope which can breed distrust; prolonging of the grieving process for the family; and undermining of the authority of the physician to achieve a timely and accurate diagnosis—this can lead to societal harm from a negotiated or inconsistent standard of death. Other practical considerations are that a homicide investigation cannot commence until the victim is officially dead and inheritance proceedings cannot commence until BD/DNC is declared.

Organ Donation

Organ donation is a complicated topic, especially when there is ambiguity regarding patient wishes. All conversations about organ donation should be done by the appropriate organ procurement agency (OPA), not the individual healthcare provider. However, the medical team has important clinical concerns to maintain organ viability, should donation be in the patient's wishes. Derangements in many organ systems may be expected but it is important to pay particular attention to hypotension and lack of heart rate variability, endocrine abnormalities (diabetes insipidus, hyperglycemia, and hypothyroidism), fluid and electrolyte abnormalities (diabetes insipidus and hypernatremia), hypothermia, and coagulopathy. It is essential for the intensivist to remember that their mandate is to support the patient currently under their care and to select what care is necessary and what is optional. After diagnosis of BD/DNC, care is transferred to the OPA intensivists with different goals.

Caring for the Family After a Diagnosis of BD/DNC

The discussion with families about a diagnosis of BD/DNC begins prior to determination of BD/DNC. Early discussion with family about the gravity of their loved one's situation can reduce the anguish that may occur with the onset of BD/DNC. At this time if a family is religious or seeking spiritual care, involvement of the hospital chaplain can be helpful to provide insight into what medical interventions may be morally required and what medical care is extraordinary or legitimately refused. There may be some value in allowing the patient's family to watch the tests conducted to establish BD/DNC to be as transparent as possible.[22–24]

Once BD/DNC is established, it is important to inform family as soon as possible (just as you would in the case of cardiopulmonary death).[25] It is best to deliver this news to the family in person, and without equivocation. The most senior member of the team, preferably the attending physician, should be the designated spokesman. Physicians and caregivers who frequently treat critically ill patients should be trained by hospital educators in these sensitive conversations. Simulation training is a helpful tool to allow caregivers to practice these conversations in a controlled environment. The family should be gathered in a quiet comfortable room to allow them to process this difficult news in private. When discussing the results of the BD/DNC examination, it is best to use the words "death" or "died" so there is no confusion and to avoid the term "brain dead." The modifier to death (brain) can give the family the impression something other than death has occurred. In addition, avoid the term "life-support" or "withdrawing life support" to refer to ventilation; at this point the ventilator is simply a machine blowing air into the lungs. For the staff, it is important to not talk to the patient as if they were alive (e.g., "I'm going to turn you now, Joe"). When discussing BD/DNC, it is important to take as much time as is needed to explain it to the family and work though all questions and doubts in a gentle, kind, and compassionate manner. Family emotions will cycle through shock, anger, guilt, and denial. It is important to acknowledge and accept these feelings and anything short of violence (which can never be tolerated). This will allow the family to be more receptive to the conversations that follow; studies show only 52% of families may understand the information given to them at the time of BD/DNC diagnosis.[26] It is important to review the hospital policy on BD/DNC and verify that it is in accordance with state and federal laws. Hospital policy should outline specific diagnostic tests to be done, who is to do them, and when to consult your ethics committee in the case of any ambiguity or family resistance.

CONCLUSION

The differentiation between cardiorespiratory death and brain death is a relatively new concept that is fraught with ethical and moral issues for both clinician and family. It is essential for a clinician to have a strong understanding of the clinical aspects of the BD/DNC examination, as well as how to approach this difficult conversation with family to not only promote confidence in the BD/DNC diagnosis but also to provide compassionate care to the newly deceased patient and their family.

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